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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/632,682	07/31/2003	Chaitan Khosla	286002022900	2700

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EXAMINER	
SAIDHA, TEKCHAND	
ART UNIT	**PAPER NUMBER**
1652	

DATE MAILED: 05/12/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/632,682	KHOSLA ET AL.	
	Examiner	Art Unit	
	Tekchand Saidha	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 April 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) *1-20 (all in-part)* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20 (all in-part)* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *7.31.2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

RD

DETAILED ACTION

1. ***Election***

Applicant's election with traverse of Group I, claims 1-20 (all in-part), drawn to recombinant E. coli host cell containing an expression system for producing desosamine as the diphosphate 6-deoxy-sugar, filed 07 April 2005, is acknowledged. The traversal is on the ground(s) that 'claim 1 is directed to a recombinant *E. coli* host cell containing an expression system for producing at least one nucleotide diphosphate 6-deoxy-sugar. Dependent claim 4 lists ten sugars that may be produced by such expression system. Thus, claim 1 is broader than claim 4. However, the Restriction Requirement only defines the groups based on each of the ten sugars and does not account for a group which contains a broader description of sugars which may be produced by an expression system defined in claim 1. Thus, it is respectfully submitted that the applicants will be prejudiced if they will not be able to claim the invention as they choose contrary to case law. Please see In re Weber 198 USPQ 328 (CCPA 1978). MPEP j 803.02 also addresses PTO practice regarding Markush-type claims, which states that members of a Markush group that are sufficiently few in number or so closely related that a search and examination of the entire claim can be made without serious burden, the examiner must examine all of the members, even though they are directed to independent and distinct inventions. Perhaps the Examiner intended to require an election of species as described in MPEP § 803.02. For these reasons, it is respectfully requested that the claims be examined in a single application.

Applicants expressly reserve their right under 35 U.S.C. § 121 to file a divisional application directed to the nonelected subject matter during the pendency of this application, or an application claiming priority from this application.

This is not found persuasive because depending upon the sugar being examined, the host cell transformed with the entire cluster of enzymes

responsible for the production for the production specific sugar are being examined. For example Applicants' election of Group I (sugar - desosamine), involving recombinant *E. coli.* transformed with desosamine biosynthetic genes from Str*eptomyces venezuelae* involve seven genes d*esI, desII, desIII, desIV, desV, desVI* and *des VIII*, which are responsible for the biosynthesis of deoxysugar, and the eighth gene (*des VII*), encodes a glycosyltransferase that apparently catalyses desosamine onto the alternate (12- and 14-membered ring) polyketide aglycone (*see* Xue et al., PNAS, USA, 95: 112111-12116, October 1998, **IDS**, page 12113, column 2, second paragraph and Figure 2, for example; see abstract also).

Similarly, the **mycarose**-biosynthesis gene of *Streptomyces fradiae* involve multiple genes (see Microbiology 146: 139-146, Bates et al. **IDS**).

Therefore, depending upon the sugar, a number of diverse gene clusters transformed into *E. coli* will have to be examined, which is further compounded by having to consider such genes from any source, as in claim 1. Therefore, members of such a Markush group are not 'sufficiently few' in number, as argued by the Applicants nor are they closely related as exemplified by the cited references above wherein depending upon the gene cluster and the biosynthetic process involved a distinct deoxysugar is produced, and searching for such a vast and diverse group of inventions would involve serious burden on the Examiner.

The requirement is still deemed proper and is therefore made FINAL.

2. ***Continuation of prior application***

This application filed under 35 USC 119(e) lacks the necessary reference to the prior application. 'This application claims the benefit of US Provisional Application No. 06/400,122, filed 07/31/2002', should be entered following the title of the invention or as the first sentence of the specification. Also, the present status of all parent applications should be included.

3. ***Priority***

Applicant's claim for domestic priority under 35 U.S.C. 119(e), filed 31 July 2002, is acknowledged.

4. **Claims withdrawn** :

Groups II-X, claims 1-20, all in-part, are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention, the requirement having been traversed.

5. ***Specification***

The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

6. ***Claim Objections***

Claims 4 & 10-13, 15- is objected to because of the following informalities: Claim 4 recite 'wherein said sugar is selected from a group consisting of desosamine, cladinose, ...mycarose, etc.'. But for 'desosamine' all other sugar recited in the claim are non-elected. Appropriate correction, deleting the non-elected subject matter, is required.

7. ***Claim Rejections - 35 USC § 112*** (first paragraph)

Enablement

Claims 1-20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a recombinant *E. coli* host cell transformed with *desI-desVIII* (eight genes) from *Streptomyces venezualae* for producing desosamine and a method of producing the polyketide as a result of expression of these genes, does not reasonably provide enablement for the producing any nucleotide diphosphate 6-deoxy-sugar or the 10 sugars listed in claim 4, by transforming *E. coli* with any of known or those yet to be discovered

gene clusters which may or may or may not be employed in the claimed host cell constructs.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with the claims. Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988))[*Ex parte* Forman [230 USPQ 546 (Bd. Pat. App. & Int. 1986)]. The Wands factors are: (a) the quantity of experimentation necessary, (b) the amount of direction or guidance presented, (c) the presence or absence of working example, (d) the nature of the invention, (e) the state of the prior art, (f) the relative skill of those in the art, (g) the predictability or unpredictability of the art, and (h) the breadth of the claim. The factors most relevant to this rejection are [the scope of the claims, unpredictability in the art, the amount of direction or guidance presented, and the amount of experimentation necessary].

The claims are drawn to encompass *E. coli* host cell for producing any nucleotide diphosphate 6-deoxy-sugar (claim 1), further expressing 6-deoxyglycosyl transferase (claim 2), an enzyme unrelated to the desosamine biosynthesis. Claim 3, further comprises an expression system for the synthesis of any polyketide, which may be compounds with diverse activities. Examples of such compounds include tetracycline, erythromycin, narbomycin, picromycin, rapamycin, spinocyn & tylosin among others. Claims 4-20, add on limitations of selected sugars, genus/species for the origin of the desosamine biosynthetic genes, genes not related to desosamine biosynthesis, methods for producing any glycosylated polyketide or 6-deoxyerythronolide B, or a method of producing erythromycin analog by culturing the host cell which further comprises an expression system for an erythromycin C 3"-O-methyltransferase.

The specification, however, only discloses recombinant *E. coli* host cell transformed with *desI-desVIII* (eight genes) from *Streptomyces venezualae* for

producing desosamine and a method for producing desosamine or the polyketide as a result of expression of *desI-desVIII* [*desVII* is also known as desosaminyltransferase]. There is no disclosure or description of the numerous embodiments which include any nucleotide diphosphate 6-deoxy-sugar or the 10 sugars listed in claim 4, by transforming *E. coli* with any of known or those yet to be discovered gene clusters which may or may not be employed in the claimed host cell constructs or the methods thereof.

Despite knowledge in the art for the production of specific nucleotide diphosphate 6-deoxy-sugar or polyketides using specific gene clusters and its expression in *E. coli*, the claims encompass *E. coli* host cells capable of expression of a variety of gene clusters, many undiscovered, in order for the production numerous sugars or polyketides. The instant specification provides guidance to recombinant *E. coli* host cell transformed with *desI-desVIII* from *Streptomyces venezualae* for producing desosamine. No guidance is provided wherein genes are added to this construct, in order that the choice of sugar or polyketide of choice can be produced. This is illustrated in the works of Pfeifer et al. [Science, March 2001, Vol. 291, pages1790-1792, IDS], which highlights the numerous bottlenecks in the production of polyketides as well the challenges encountered in the production of complex polyketides and its functional expression in *E. coli* (see page 1790, columns 1-3). This exemplification of the biosynthesis of complex polyketides will indeed be applicable to the production of specific nucleotide diphosphate 6-deoxy-sugar as well, since the production of the sugar involves the same cluster of genes. Therefore the guidance provided is minimal and applies only to the exemplified species and which can not be extrapolated to the large genus claimed.

Since it is <u>not</u> routine in the art to engage in *de novo* experimentation to make or transform E. coli with complex metabolic gene clusters where the expectation "of success is unpredictable", the skilled artisan would require additional guidance in order to make and use transformed E. coli and methods

based thereof, in a manner reasonably commensurate with the scope of the claims. Without such guidance, the experimentation left to those skilled in the art is undue.

8. ***Written Description***

Claims 1-20 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-20 are directed to recombinant *E. coli* host cell transformed with gene clusters for the production any nucleotide diphosphate 6-deoxy-sugar or the 10 sugars listed in claim 4, by transforming *E. coli* with any of known or those yet to be discovered gene clusters, the claimed genus. The claims are further drawn to encompass *E. coli* host cell for producing any nucleotide diphosphate 6-deoxy-sugar (claim 1), further expressing 6-deoxyglycosyl transferase (claim 2), an enzyme unrelated to the desosamine biosynthesis. Claim 3, further comprises an expression system for the synthesis of any polyketide, which may be compounds with diverse activities. Examples of such compounds include tetracycline, erythromycin, narbomycin, picromycin, rapamycin, spinocyn & tylosin among others. Claims 4-20, add on limitations of selected sugars, genus/species for the origin of the desosamine biosynthetic genes, genes not related to desosamine biosynthesis, methods for producing any glycosylated polyketide or 6-deoxyerythronolide B, or a method of producing erythromycin analog by culturing the host cell which further comprises an expression system for an erythromycin C 3"-O-methyltransferase.

The specification exemplifies a single species in recombinant *E. coli* host cell transformed with gene clusters for *desI-desVIII* from *Streptomyces venezualae* for producing desosamine and a method of producing the polyketide as a result of expression of these genes, does not reasonably provide

enablement for the producing any nucleotide diphosphate 6-deoxy-sugar or the 10 sugars listed in claim 4, by transforming *E. coli* with any of known or those yet to be discovered gene clusters which may or may or may not be employed in the claimed host cell constructs.

The specification does not teach the kind of complex gene clusters for the synthesis of desosamine from any source, and their expression in *E. coli.* No structural information, beyond the prior art characterization of *desI-desVIII* from *Streptomyces venezualae* has been provided by Applicants which would indicate that they had possession of the claimed genus. Therefore, many non-functional transformed E. coli host cell and methods based thereof are within the scope of the claimed genus.

There is no disclosure of any particular structure to function/activity relationship in the single disclosed species to other species where such cluster genes may be transformed into an *E. coli* host as no clear cut linearized sequences of the genes from other sources have been shown or where wherein the gene structure is apparent. No generalized protocol can be deduced from the instant disclosure that would be applicable for constructing any *E. coli* host cell gene transformation or methods based thereof as claimed. Without a clear description of how one can extrapolate the 1 species construct to other gene constructs having the broad characteristics as claimed, the specification lack the written description requirement.

Therefore, Applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise, and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention. Therefore, the written description requirement is not satisfied.

9. ***Claim Rejections - 35 USC § 112*** (second paragraph)

Claims 2-5, 12-19 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 2, 4, 12 and17 recite the enzyme '6-deoxyglycosyl transferase'. A search of the patent and non-patent data bases has not allowed for the search of the enzyme based on the name used, accept for Applicants' own work. The claim is indefinite for because the enzyme name used, does not appear to be the correct or accepted name in the art. Is this the same as '*des VII*' or glycosyltrasferase'. Clarification is requested regarding EC number, alternate names, designated name, etc.

Claims 3, 5, 13-16 & 18-19 are included in the rejection for failing to correct the defect present in the base claim(s).

10. Claims 13-16 & 19 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 13, line 1, recites 'erm'. The claim is indefinite, for it is unclear what 'erm' stands for. If an abbreviation, the first use of an abbreviation must be spelled out, which may be abbreviated in the subsequent claims.

10. ***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claim 1, 4, 5-9 & 20 are rejected under 35 U.S.C. 102(e) as being anticipated by Ashley et al. (USP 6,117,659, May 27 1999). Ashley et al. teach the recombinant expression of *desI-desVIII* genes from *Streptomyces venezuelae*

[des VII is also known as desosaminyltransferase] into a host cell, including the preferred host cell E. coli [see column 34, especially lines 40-67; column 35-39 showing sequences of des genes; and column 49, lines 12-33 – showing the preferred host cells including *E. coli.*]. All claim limitations being taught, the reference anticipates the claims.

12. Claim 1, 4, 5-9 & 20 are rejected under 35 U.S.C. 102(b) as being anticipated by Xue et al. [PNAS, USA, Vol. 95, pages 12111-12116, October 1998). Xue et al. teach the recombinant expression of *desI-desVIII* genes from *Streptomyces venezuelae [des VII is also known as desosaminyltransferase]* into a host cell, with *E. coli* an the cloning host [see Abstract, Materials & Methods, Result]. The genetic locus for desosamine biosynthesis and glycosyl transfer are immediately downstream of *pikA* is described. Seven genes *desI, desII, desIII, desIV, desV, desVI & desVIII* are taught to be responsible for the biosynthesis of deoxysugar, and the eight gene, *desVII,* encodes a glycosyl transferase. All claim limitations being taught, the reference anticipates the claims.

13. No claim is allowed.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tekchand Saidha whose telephone number is (571) 272 0940. The examiner can normally be reached on 8.30 am - 5.00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on (571) 272 0928. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through

Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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